Claims

We claim:

1. A stabilized peptide formulation, either in a solution or in a suspension, comprising:

   (a) a peptide containing at least one histidine residue;

   (b) a transition metal salt; and

   (c) a pharmaceutically acceptable organic solvent.

2. The formulation of claim 1, wherein said peptide is selected from the group consisting of the peptide hormone superfamily containing PACAP, PACAP-like peptides, VIP, glucagon, glucagon-like peptides, secretin, helodermin, exendin-4, and functionally equivalent variants thereof.

3. The formulation of claim 1, wherein said peptide is PACAP 66 (SEQ ID NO: 1).

4. The formulation of claim 1, wherein said histidine residue is a terminal histidine residue.

5. The formulation of claim 1, wherein said peptide is selected from the group consisting of adrenocorticotropic hormone, angiotensins, renin substrate tetradecapeptide, natriuretic peptides, gastrointestinal peptides, luteinizing hormone releasing hormone, melanocyte sitmulating hormone, and neurotensin, and parathyroid hormone.

6. The formulation of claim 1, wherein said transition metal salt is a salt of a transition metal selected from the group consisting of zinc, copper, iron, manganese, nickel and cobalt.

7. The formulation of claim 6, wherein said transition metal salt is a zinc salt.

8. The formulation of claim 1, wherein said organic solvent is selected from the group consisting of DMSO, 1-methyl-2-pyrrolinidone, propanol, propylene glycol, glycerol acetate, monothioglycerol, acetic acid, diethanolamine, benzyl alcohol, ethyl

lactate, glycerol formal, N-methylpyrrolidone, polyethyleneglycol 400, and isopropyl myristate.

9. The formulation of claim 1, wherein said organic solvent is a mixture of two or more organic solvents selected from the group consisting of DMSO, 1-methyl-2-pyrrolinidone, propanol, propylene glycol, glycerol acetate, monothioglycerol, acetic acid, diethanolamine, benzyl alcohol, ethyl lactate, glycerol formal, N-methylpyrrolidone, polyethyleneglycol 400, and isopropyl myristate.

10. The formulation of claim 8, wherein said organic solvent is DMSO, 1-methyl-2-pyrrolinidone, or propanol.

11. A stabilized peptide formulation, either in a solution or in a suspension, comprising:

(a) PACAP 66 (SEQ ID NO: 1) and/or salts thereof;

(b) $ZnCl_2$; and

(c) a pharmaceutically acceptable organic solvent.

12. The stabilized peptide formulation of claim 11, wherein said organic solvent is selected from the group consisting of DMSO, 1-methyl-2-pyrrolinidone, propanol, propylene glycol, glycerol acetate, monothioglycerol, acetic acid, diethanolamine, benzyl alcohol, ethyl lactate, glycerol formal, N-methylpyrrolidone, polyethyleneglycol 400, and isopropyl myristate.

13. The stabilized peptide formulation of claim 12, wherein said organic solvent is DMSO, 1-methyl-2-pyrrolinidone or propanol.

14. The formulation of claim 11, wherein said organic solvent is a mixture of two or more organic solvents selected from the group consisting of DMSO, 1-methyl-2-pyrrolinidone, propanol, propylene glycol, glycerol acetate, monothioglycerol, acetic acid, diethanolamine, benzyl alcohol, ethyl lactate, glycerol formal, N-methylpyrrolidone, polyethyeneglycol 400, and isopropyl myristate.

15. The formulation of claim 11, wherein said $ZnCl_2$ is at a $ZnCl_2$:peptide molar ratio of above 0.1 in said organic solvent.

16. The formulation of claim 11, wherein said PACAP 66 and/or salts thereof are at a concentration of above 0.1 mg/mL of said organic solvent.

17. A stabilized peptide formulation, comprising a dried mixture of an acid and a peptide containing at least one asparagine residue.

18. The formulation of clam 17, wherein said peptide is PACAP 66 (SEQ ID NO: 1).

19. The formulation of claim 17, wherein said acid is an inorganic acid.

20. The formulation of claim 19, wherein said inorganic acid is selected from HCl and H_3PO_4.

21. The formulation of claim 17, wherein said acid is TFA.

22. The formulation of claim 17, wherein said formulation is freeze-dried or spray-dried.

23. The formulation of claim 17, further comprising a transition metal salt.

24. The formulation of claim 23, wherein said transition metal salt is a salt of a transition metal selected from the group consisting of zinc, copper, iron, manganese, nickel and cobalt.

25. The formulation of claim 24, wherein said transition metal is zinc.

26. A stabilized peptide formulation, comprising a dried mixture of an acid and PACAP 66 (SEQ ID NO: 1) and/or a salt thereof.

27. The formulation of claim 26, wherein said acid is TFA.

28. The formulation of claim 26, wherein said acid is an inorganic acid.

29. The formulation of claim 28, wherein said inorganic acid is selected from HCl and H_3PO_4.

30. The formulation of claim 26, wherein a molar ratio of said acid to said PACAP 66 and/or a salt thereof is above 0.1.

31. The formulation of claim 26, further comprising a transition metal salt.

32. The formulation of claim 31, wherein said transition metal salt is a salt of a transition metal selected from the group consisting of zinc, copper, iron, manganese, nickel and cobalt.

33. The formulation of claim 32, wherein said transition metal is zinc.

34. A stabilized peptide formulation, comprising a dried mixture of a transition metal salt and a peptide containing at least one histidine residue.

35. The formulation of claim 34, further comprising a pharmaceutically acceptable organic solvent.

36. The formulation of claim 35, wherein said organic solvent is selected from the group consisting of DMSO, 1-methyl-2-pyrrolinidone, propanol, propylene glycol, glycerol acetate, monothioglycerol, acetic acid, diethanolamine, benzyl alcohol, ethyl lactate, glycerol formal, N-methylpyrrolidone, polyethyleneglycol 400, and isopropyl myristate.

37. The formulation of claim 36, wherein said organic solvent is DMSO, 1-methyl-2-pyrrolinidone or propanol.

38. The formulation of claim 35, wherein said organic solvent is a mixture of two or more organic solvents selected from the group consisting of DMSO, 1-methyl-2-pyrrolinidone, propanol, propylene glycol, glycerol acetate, monothioglycerol, acetic acid, diethanolamine, benzyl alcohol, ethyl lactate, glycerol formal, N-methylpyrrolidone, polyethyleneglycol 400, and isopropyl myristate.

39. The formulation of claim 34, wherein said peptide is selected from the consisting of the peptide hormone superfamily containing PACAP, PACAP-like peptides, VIP, glucagon, glucagon-like peptides, secretin, helodermin, exendin-4, and functionally equivalent variants thereof.

40. The formulation of claim 34, wherein said peptide is PACAP 66 (SEQ ID NO: 1).

41. The formulation of claim 34, wherein said peptide is selected from the group consisting of adrenocorticotropic hormone, angiotensins, renin substrate tetradecapeptide, natriuretic peptides, gastrointestinal peptides, luteinizing hormone

releasing hormone, melanocyte sitmulating hormone, and neurotensin, and parathyroid hormone.

42. The formulation of claim 34, wherein said transition metal salt is a salt of a transition metal selected from the group consisting of zinc, copper, iron, manganese, nickel and cobalt.

43. The formulation of claim 42, wherein said transition metal salt is a zinc salt.

44. A process for preparing a stabilized peptide formulation, comprising the steps of:

(a) preparing an acid solution of acid and water;

(b) cooling said acid solution to below room temperature;

(c) mixing said cooled acid solution and a peptide containing at least one asparagine residue to create a cooled mixture; and

(d) drying said cooled mixture.

45. The process of claim 44, wherein said acid is an inorganic acid.

46. The process of claim 45, wherein said inorganic acid is selected from HCl and H_3PO_4.

47. The process of claim 44, wherein said acid is TFA.

48. The process of claim 44, wherein said peptide is PACAP 66 (SEQ ID NO: 1) and/or a salt thereof.

49. The process of claim 48, wherein a molar ratio of said acid to said PACAP 66 and/or a salt thereof is above 0.1

50. The process of claim 44, wherein said drying step is freeze-drying or spray-drying.

51. The process of claim 44, further comprising adding a transition metal salt to said cooled mixture before drying said cooled mixture.

52. The process of claim 51, wherein said transition metal salt is a salt of a transition metal selected from the group consisting of zinc, copper, iron, manganese, nickel and cobalt.

53. The process of claim 52, wherein said transition metal is zinc.

54. A process for preparing a stabilized peptide formulation, comprising the steps of:

(a) mixing an aqueous solution containing a transition metal salt with a peptide containing at least one histidine residue; and

(b) drying said mixture.

55. The process of claim 54, wherein said peptide is selected from the group consisting of the peptide hormone superfamily containing PACAP, PACAP-like peptides, VIP, glucagon, glucagon-like peptides, GRF, secretin, helodermin, exendin-4, and functionally equivalent variants thereof.

56. The process of claim 54, wherein said peptide is PACAP 66 (SEQ ID NO: 1).

57. The process of claim 54, wherein said peptide is selected from the group consisting of adrenocorticotropic hormone, angiotensins, renin substrate tetradecapeptide, natriuretic peptides, gastrointestinal peptides, luteinizing hormone releasing hormone, melanocyte sitmulating hormone, and neurotensin, and parathyroid hormone.

58. The process of claim 54, wherein said transition metal salt is a salt of a transition metal selected from the group consisting of zinc, copper, iron, manganese, nickel and cobalt.

59. The process of claim 58, wherein said transition metal salt is a zinc salt.

60. The process of claim 54, further comprising the step of adding a pharmaceutically acceptable organic solvent to said dried mixture.

61. The process of claim 60, wherein said organic solvent is selected from the group consisting of DMSO, 1-methyl-2-pyrrolinidone, propanol, propylene glycol, glycerol acetate, monothioglycerol, acetic acid, diethanolamine, benzyl alcohol, ethyl

lactate, glycerol formal, N-methylpyrrolidone, polyethyeneglycol 400, and isopropyl myristate.

62. The process of claim 60, wherein said organic solvent is a mixture of two or more organic solvents selected from the group consisting of DMSO, 1-methyl-2-pyrrolinidone, propanol, propylene glycol, glycerol acetate, monothioglycerol, acetic acid, diethanolamine, benzyl alcohol, ethyl lactate, glycerol formal, N-methylpyrrolidone, polyethyeneglycol 400, and isopropyl myristate.

63. The process of claim 61, wherein said organic solvent is DMSO, 1-methyl-2-pyrrolinidone, or propanol.

64. The process of claim 54, wherein said histidine residue is a terminal histidine residue.

65. The process of claim 54, wherein said drying step is freeze-drying or spray-drying.